Docket No.: 022290.0116C1US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Valerie Legrand et al.

Application No.: 10/826,690 Confirmation No.: 9585

Filed: April 19, 2004 Art Unit: 1618

For: MICROPARTICULATE ORAL GALENICAL FORM FOR THE DELAYED AND CONTROLLED RELEASE OF PHARMACEUTICAL ACTIVE PRINCIPLES

Examiner: L. Schlientz

DECLARATION OF CATHERINE CASTAN

1. My name is Catherine CASTAN.

2. I have been an employee of Flamel Technologies, S.A. since 1992.

3. My position at Flamel Technologies, S.A. is Director of Galenic Department.

4. I have a Ph.D. in Polymer Chemistry.

5. I have worked in the area of pharmaceutical compositions for 21 years.

6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for delayed and controlled release of active principles.

7. I supervised Pierre DANNER, Jean-Luc TERRANCLE and Noëlle VILLARD, who prepared the below three different compounds in accordance with the U.S. Application No.: 10/826,690 invention.

8. To the best of my knowledge, the information below is an accurate description of how these three compounds were prepared, and their release profiles measured.

9. Compound 1 was formed of the active ingredient losartan, polymers A Eudragit L100-55 and Eudragit S100, and the hydrophobic compound Lutritab (hydrogenated cotton seed oil). Compound 1 has a B/A of 0.66.

10. Compound 2 was formed of the active ingredient losartan, polymer A Eudragit L100-55, and the hydrophobic compound Lutritab (hydrogenated cotton seed oil). Compound 2 has a B/A of 0.66.

11. Compound 3 was formed of the active ingredient of ramipril, polymer A hydroxypropylmethylcellulose phthalate (HPMCP) and the hydrophobic compound Lutritab (hydrogenated cotton seed oil). Compound 3 has a B/A of 0.66.

12. Figures 1 – 3 below show all three compounds had a release profile such that at pH 1.4 the release starts after a lag-time comprised between 0 and 5h, and at pH 6.8 the release starts immediately without any lag time.

13. Compound 1

a. Compound 1 was prepared as follows:

i. 135 g of hydroxypropylcellulose (Klucel® EF) are dissolved in 3150 g of isopropanol. 1215 g of losartan potassium are then dispersed in the solution. The suspension was entirely sprayed onto 150g of cellulose spheres (Celphere® SCP-100 from Asahi Kasei) in a fluid bed spray coater apparatus Glatt® GPCG1.1. The obtained microparticles are sieved on screens 150 and 500 µm. Microparticles with size comprised between 150 and 500 µm are retained.

ii. 45.77 g of poly (methacrylic acid, ethyl acrylate) 1 : 1 (Eudragit® L100-55), 91.54 g of poly (methacrylic acid, methylmethacrylate) 1 : 2 (Eudragit®S100) and 91.54 g of hydrogenated cottonseed oil (Lubritab®) are dissolved in 2059.62 g of hot ispropanol. The solution is sprayed entirely onto 425 g of the above prepared microparticles in a fluid bed spray coater apparatus Glatt® GPCG1.1 with inlet temperature 50°C, spraying rate about 11.3 g per min and atomization pressure 1.6 bar.

b. Compound 1 was tested as follows:

i. The microcapsules were tested in a type II dissolution apparatus according to the Pharmacopoeia in 900 ml of dissolution medium maintained at 37.0 ± 0.5 °C, agitated by a rotating paddle at 100 rpm. Two different dissolution media were used in order to evidence the double release mechanism:

1. Dissolution medium: HCl solution with pH = 1.4
2. Dissolution medium: monobasic potassium phosphate buffer 0.05M pH 6.8

c. The release profile of Compound 1 is shown in Figure 1. The release profile obtained at pH 1.4 shows that, in acidic medium similar to gastric pH, the release starts after a lag-time comprised between 0 and 5h. Thus the drug is released in the stomach after a lag time. The release profile obtained at pH 6.8 shows that the release starts immediately without any lag time and the kinetics is accelerated compared to that obtained in pH 1.4.

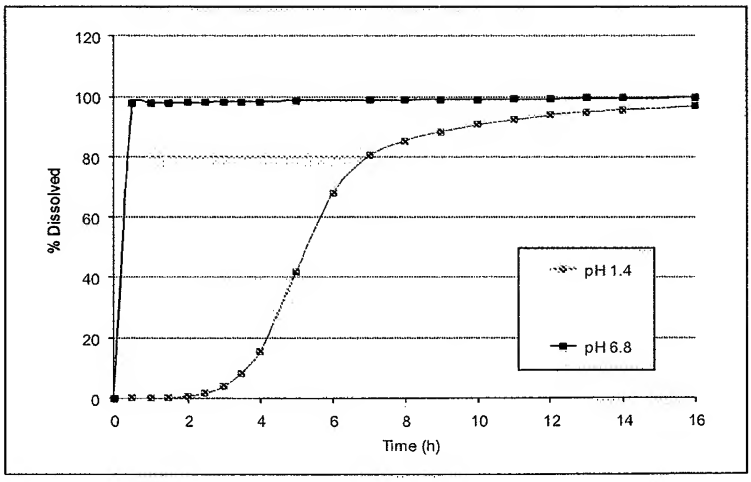

Figure 1

14. Compound 2

a. Compound 2 was prepared as follows:

i. 180 g hydroxypropylcellulose (Klucel® EF) were dissolved in 2255 g acetone and 405 g isopropanol. 1620 g losartan potassium were then dispersed in the solution. The suspension was entirely sprayed onto 200g of cellulose spheres (Celphere® SCP-100 from Asahi Kasei) in a fluid bed spray coater apparatus Glatt® GPCG1.1. The obtained microparticles were sieved on screens 150 and 500 μm. Microparticles with size comprised between 150 and 500 μm were retained.

ii. 147 g poly (methacrylic acid, ethyl acrylate) 1 : 1 (Eudragit® L100-55) and 98 g hydrogenated cottonseed oil (Lubritab®) were dissolved in 2205 g hot ispropanol. The solution was sprayed entirely onto 455 g of the above prepared microparticles in a fluid bed spray coater apparatus Glatt® GPCG1.1 with inlet temperature 51°C, spraying rate about 11.7 g per min and atomization pressure 1.6 bar.

b. Compound 2 was tested as follows:

i. The microcapsules were tested in a type II dissolution apparatus according to the Pharmacopoeia in 900 ml of dissolution medium maintained at 37.0 ± 0.5 °C, agitated by a rotating paddle at 100 rpm. Two different dissolution media were used in order to evidence the double release mechanism:

1. Dissolution medium: HCl solution with pH = 1.4
2. Dissolution medium: monobasic potassium phosphate buffer 0.05M pH 6.8

c. The release profile of Compound 2 is shown in Figure 2. The release profile obtained at pH 1.4 shows that, in acidic medium similar to gastric pH, the release starts after a lag-time comprised between 0 and 5h. Thus the drug is released in the stomach after a

lag time. The release profile obtained at pH 6.8 shows that the release starts immediately without any lag time and the kinetics is accelerated compared to that obtained in pH 1.4.

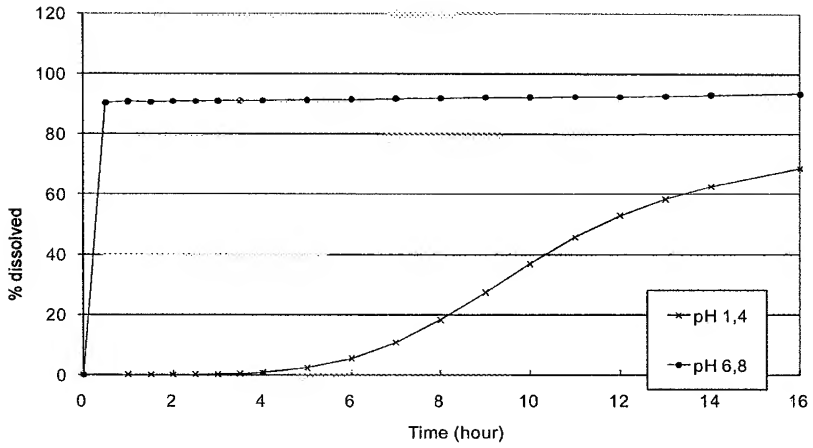

Figure 2

15. Compound 3

a. Compound 3 was prepared as follows:

i. 45 g hydroxypropylmethylcellulose (Methocel® E5 premium LV from Dow) was dissolved in 1350 g water. 105 g ramipril was then dispersed in the solution. The suspension was entirely sprayed onto 1200g cellulose spheres (Celphere™ CP305 from Asahi Kasei) in a fluid bed spray coater apparatus Glatt® GPCG1.1. The obtained microparticles were sieved on screens 200 and 630 µm. Microparticles with size comprised between 200 and 630 µm were retained. 150g hydroxypropylmethylcellulose (Methocel® E5 premium LV from Dow) were dissolved in 1992.86 g water and sprayed on the above prepared microparticles.

ii. 48.84 g poly Hydroxypropylmethylcellulose phthalate (HP-50 from Shin-Etsu) and 32.56 g hydrogenated cottonseed

oil (Lubritab®) were dissolved in 695.93 g hot ispropanol and 36.63 g water. The solution was sprayed entirely onto 500 g of the above prepared microparticles in a fluid bed spray coater apparatus Glatt® GPCG1.1 with inlet temperature 50°C, spraying rate about 10 g per min and atomization pressure 2.0 bar.

b. Compound 3 was tested as follows:

i. The microcapsules were tested in a type II dissolution apparatus according to the Pharmacopoeia in 900 ml of dissolution medium maintained at 37.0 ± 0.5 °C, agitated by a rotating paddle at 100 rpm. Two different dissolution media were used to evidence the double release mechanism:

1. Dissolution medium: HCl solution with pH = 1.4
2. Dissolution medium: monobasic potassium phosphate buffer 0.05M pH 6.8

ii. The release profile of Compound 3 is shown in Figure 3 below. The release profile obtained at pH 1.4 shows that, in acidic medium similar to gastric pH, the release starts after a lag-time comprised between 0 and 5h. Thus the drug is released in the stomach after a lag time. The release profile obtained at pH 6.8 shows that the release starts immediately without any lag time and the kinetics is accelerated compared to that obtained in pH 1.4.

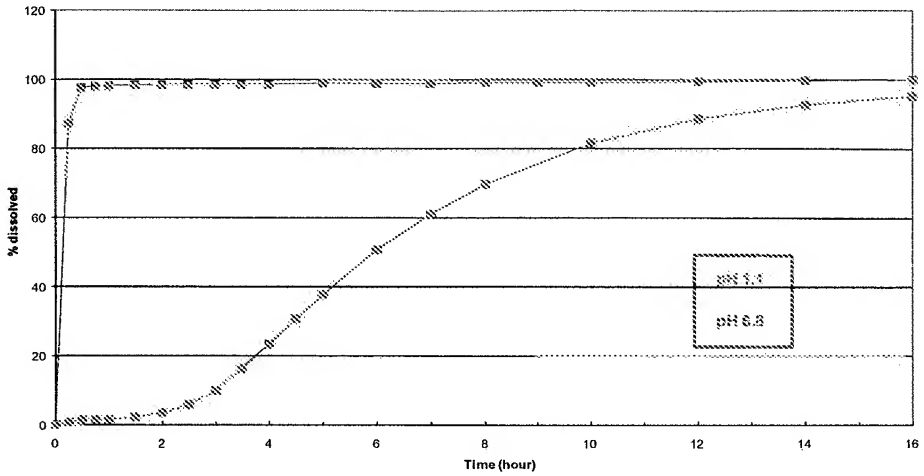

Figure 3

16. I declare that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.

Catherine CASTAN Dec. 18th 2009
Date